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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,905	09/20/2005	Dionysios Papaioannou	13907.02	7153

25570 7590 09/17/2007
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EXAMINER	
JARRELL, NOBLE E	
ART UNIT	**PAPER NUMBER**
1624	

NOTIFICATION DATE	DELIVERY MODE
09/17/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/549,905	PAPAIOANNOU ET AL.	
	Examiner	Art Unit	
	Noble Jarrell	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) *6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-7* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 September 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *July 21, 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group I in the reply filed on 8/22/2007 is acknowledged. The traversal is on the ground(s) that restriction is improper. This is not found persuasive because there is no unity of invention due to number of polyamine cores and retinoic acid derivatives. Three different types of broad polyamine cores and the four types of retinoic acid derivatives exist in claim 1. In the elected group itself, there are 8 unique polyamine cores. In the non-elected polyamine cores, there are 6 different polyamine cores. Taking all of this into consideration, there are 4 (for the retinoic acid derivatives) times 14 (unique polyamine cores), which equals 56 combinations for the structure of claim 1. In addition, the R group attached to the molecule (when at least two R groups are attached) does not have to be the same. Thus, there is much variability to the structure of claim 1. Each different possibility requires a separate structural query and may be classified differently, depending on what is present within each combination.

The requirement is still deemed proper and is therefore made FINAL.

Claim Objections

2. Claim 1 is objected to because of the following informalities: it contains non-elected subject material. Appropriate correction is required.

Oath/Declaration

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
It does not identify the citizenship of each inventor.

It does not identify the city and either state or foreign country of residence of each inventor. The residence information may be provided on either an application data sheet or supplemental oath or declaration.

It was not executed in accordance with either 37 CFR 1.66 or 1.68. The applicant named Dionysios Tsambaos has not signed the oath.

Specification

4. The use of the trademarks Buchi, Perkin-Elmer, and Bruker (all on page 16) have been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 7 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds and the synthetic methods of making the same, does not reasonably provide enablement for pharmaceutical compositions of the claimed compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants adequately show that compounds of claim 1 can be produced by the methods depicted in figures 1-12. Applicants also show *in vitro* testing of the prepared compounds

against peripheral blood mononuclear cells. However, just because compounds work *in vitro* does not mean that the compounds work *in vivo*. Claim 7 claims pharmaceutical compositions, which means the compounds work *in vivo*. Giuseppe et al. (*Expert Opinion on Therapeutic Patents*, **1997**, *7(4)*, 307-323) discusses unpredictability of predicting the efficacy of a compound working *in vitro* and *in vivo*. Compound 6 (page 311) was found to work as an *in vitro* NK_3-selective antagonist, but was found to not work *in vivo* because of its peptide nature and associated poor pharmacokinetic properties. Hence the compound was a candidate for preclinical developmental studies. In addition, applicants do not show compositions of the products with inert carriers, excipients, or adjuvants, is not shown in the specification. Applicants do not show that these compounds can be present in compositions, and are thus not enabled for compositions.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to polyamines bound to retinoic acid derivatives through amide functional groups.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Compounds of the instant invention can be considered novel. However, Giuseppe et al. show that just because a compound is effective *in vitro* does not mean the compound will function *in vivo*.

(5) The relative skill of those in the art:

One or ordinary skill in the art is a chemist familiar with the synthetic techniques depicted in the figures.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for the preparation of the elected group of compounds and their *in vitro* testing.

However, the specification does not provide guidance that the compounds work *in vivo*.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to claim 7 and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

7. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of diisopropylethylamine in the acylation of the primary and secondary amine groups, does not reasonably provide enablement for the use of any tertiary amine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Examples 3, 4, and 6 of the specification show the use of diisopropylethylamine in the formation of the different products. However, not all tertiary amines are non-nucleophilic ("Amines",

http://users.ox.ac.uk/~mwalter/web_05/year1/organinitrogen/amines.html, accessed September 7, 2007). Although tertiary amines have drastically reduced nucleophilic character and tend to react as bases rather than nucleophiles, tertiary amines can still act as nucleophiles. Take, for example, the reaction between $N(CH_3)_3$ and methyl iodide. The product of this reaction is $[N(CH_3)_4]^+I^-$. In this instance, a tertiary amine is behaving as a nucleophile. Therefore, not all tertiary amines are non-nucleophilic.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to retinoids conjugated to polyamines.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The compounds of the elected group are considered novel.

(5) The relative skill of those in the art:

One of ordinary skill in the art is a chemist experienced in amide couplings.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for the use of diisopropylethylamine as a base in the acylation of the primary and secondary amines.

However, the specification does not provide guidance for the scope of tertiary amines provided in claim 4.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to claim 4 and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 2-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 2 sets forth three steps, instead of two steps, as it says in the preamble. What is the phrase "with the as above obtained compounds" of step b referencing, the products of claim 1 or the product of step a? As a result, claims 3-6 are rendered unclear because they depend on claim 2. Claim 4 is unclear additionally because the term "effected" is unclear. "Effected" is the noun form of "affected" and it unclear what meaning the term has in claim 4. Do applicants intend that the primary amine functions can be derivatized with carboxylic acid functional groups? In addition, what do applicants mean by "activated carboxylic acid derivative known to acylate selectively primary amino functions"? What derivative of a carboxylic acid is the claim referring to?

Claim Objections

10. Claim 6 is objected to under 37 CFR 1.75(c) as being in improper form because it is a multiple dependent claim under claims 1 and 2, not claims 1 or 2. See MPEP § 608.01(n). Accordingly, claim 6 not been further treated on the merits.

Allowable Subject Matter

11. The elected group and species as well as the synthetic methods shown in the figures are considered novel.

12. The following is a statement of reasons for the indication of allowable subject matter: Manfredini et al. report the closest prior art (*Journal of Medicinal Chemistry*, **1997**, *40*, 3651-57, included in IDS). Manfredini et al. report structure 14 on page 3852, this structure does not anticipate the elected group because the polyamine portion of the molecule contains 2 nitrogens, whereas each polyamine portion of the elected group contains at least 3 nitrogens.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Noble Jarrell whose telephone number is (571) 272-9077. The examiner can normally be reached on M-F 7:30 A.M - 6:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Noble Jarrell /NJ/

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